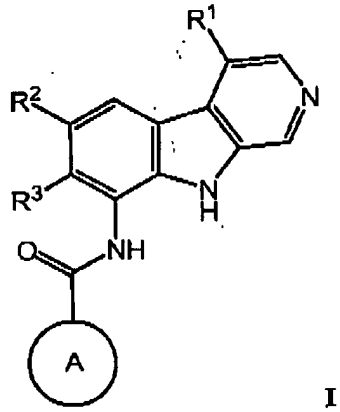
Practitioner's Docket No. MPI03-043P1RNRCEM

In the Claims:

1. (Previously Amended) A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a morpholinyl ring that is substituted by (i) $-C(R^9)_3$, –W-G, or –G, (ii) 0-4 R^{6b} and (iii) 0-1 oxo groups on a ring carbon;

each R^{6a} is independently selected from C_{1-6} aliphatic, halo, alkoxy, or amino;

each R^{6b} is independently selected from C_{1-3} aliphatic or $-N(R^7)_2$, and two R^{6b} on the same or an adjacent carbon optionally are taken together with the intervening carbon(s) to form a 5-6 membered ring having 1-2 ring heteroatoms selected from N, O or S;

W is –Q-, –Q-C(O)-, $-C(R^9)_2-C(R^9)(R^{12})-$, or $-C(R^9)_2-[C(R^9)(R^{12})]_2-$;

Q is $-C(R^9)_2-$ or $-C(R^9)_2C(R^9)_2-$;

G is –OH, $-NR^4R^5$, $-N(R^9)CONR^4R^5$, $-N(R^9)SO_2(C_{1-3}$ aliphatic), $-N(R^9)COCF_3$, $-N(R^9)CO(C_{1-6}$ aliphatic), $-N(R^9)CO$(heterocyclyl), $-N(R^9)CO$(heteroaryl), $-N(R^9)CO$(aryl), a 3-7 membered heterocyclyl ring, or a 5-6 membered heteroaryl, wherein each of the heteroaryl, aryl and heterocyclyl moieties of G is optionally substituted by 1-3 R^{10};

R^1 is hydrogen, halo, C_{1-3} aliphatic, amino, cyano, $(C_{1-3}$ alkyl$)_{1-2}$ amino, C_{1-3} alkoxy, $-CONH_2$, $-NHCOCF_3$, or $-CH_2NH_2$;

R^2 is hydrogen, halo, C_{1-3} aliphatic, $-CF_3$;

R^3 is hydrogen, halo, C_{1-6} aliphatic, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, or $(C_{1-6}$ alkyl$)_{1-2}$ amino;

R^4 is hydrogen, 3-7 membered heterocyclyl, or C_{1-6} aliphatic;

R^5 is hydrogen, C_{1-6} aliphatic group or a 3-7 membered heterocyclic ring having 1-2 ring heteroatoms selected from N, O, or S, wherein R^5 is optionally substituted by halo, $-OR^7$, -CN, $-SR^8$,

$-S(O)_2R^8$, $-S(O)_2N(R^7)_2$, $-C(O)R^7$, $-CO_2R^7$, $-N(R^7)_2$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)CO_2R^8$, or $-N(R^7)C(O)N(R^7)_2$;

each R^7 is independently selected from hydrogen or C_{1-4} aliphatic, or two R^7 on the same nitrogen atom are taken together with the nitrogen to form a 5-6 membered heteroaryl or heterocyclyl ring;

each R^8 is independently selected from C_{1-4} aliphatic;

each R^9 is independently selected from hydrogen or C_{1-3} aliphatic;

each R^{10} is independently selected from oxo, $-R^{11}$, $-T-R^{11}$, or $-V-T-R^{11}$;

each R^{11} is independently selected from C_{1-6} aliphatic, halo, $-S(O)_2N(R^7)_2$, $-OR^7$, -CN, $-SR^8$, $-S(O)_2R^8$, $-C(O)R^7$, $-CO_2R^7$, $-N(R^7)_2$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)CO_2R^7$, or $-N(R^7)C(O)N(R^7)_2$;

T is a straight or branched C_{1-4} alkylene chain;

V is –O-, $-N(R^7)-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, or $-CO_2-$; and

R^{12} is hydrogen, C_{1-6}aliphatic, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl.

Claims 2-8. (Previously canceled)

9. (Previously Amended) The compound of claim 1 where the –W-G or $-C(R^9)_3$ substituent on Ring A is ortho to the position where the beta-carboline portion is attached.

Claims 10-16. (Previously canceled)

17. (Original) A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

18-27. (Previously canceled)

28. (Original) A compound of formula IV:

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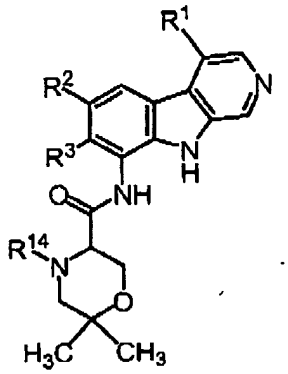


IV

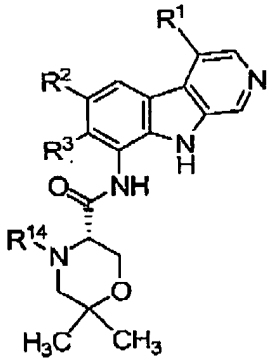
where R^{14} is an amino protecting group or hydrogen;

R^1 is hydrogen, halo, C_{1-3} aliphatic, amino, cyano, $(C_{1-3}$ alkyl$)_{1-2}$ amino, C_{1-3} alkoxy, $-CONH_2$, $-NHCOCF_3$, or $-CH_2NH_2$;

R^2 is hydrogen, halo, C_{1-3} aliphatic, $-CF_3$; and

R^3 is hydrogen, halo, C_{1-6} aliphatic, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, or $(C_{1-6}$ alkyl$)_{1-2}$ amino.

29. (Previously amended) The compound of claim 28, wherein the compound is represented by formula (*S*)-IV:



30-34. (Previously canceled).

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RESPONSE

Claims 1, 9, 17, 28, and 29 are currently pending. Applicants reserve the right to pursue the subject matter of any canceled claims in continuation or divisional applications.

Rejection under 35 U.S.C. § 103(a):

The Examiner has maintained the rejection of claims 1, 9, and 17 as being unpatentable over Castro *et al.* Specifically, the Examiner states that the difference between the prior art and the claims at issue is that the prior art provides an unsubstituted ring A, but ring A of the instant claims is substituted by at least one of $C(R^9)_3$, W-G, or G, wherein $C(R^9)_3$ can be methyl. The Examiner further states that the substitution of a methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results and that the motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (i.e., inhibitors of IKK).

In response to the arguments presented by Applicants in the Office Action Response dated August 21, 2007, and July 9, 2008, the Examiner has asserted that these arguments are not persuasive and asserts that (1) the motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity; (2) the reasonable expectation of success is seen in that it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results; and (3) the prior art teaches and suggests all of the claim limitations as Castro *et al* disclose the compound 35 and registry number 590398-98-4 useful to inhibit IKK for the treatment of certain inflammatory diseases and the only difference between the prior art and the claims at issue is that the prior art provides an unsubstituted A ring wherein ring A of the instant claims is substituted by at least one of $-C(R^9)_3$, W-G, or G, wherein $-C(R^9)_3$ can be methyl. See Office Action dated 01/09/2008, pp. 3-4.

Applicants respectfully disagree and maintain that that the Examiner has not established a *prima facie* case of obviousness and thus claims 1, 8, 9 and 17 are not obvious over Castro *et al.*

As stated in MPEP § 2142, in order to establish a *prima facie* case of obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine the teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success *must both be found in the prior art, and not based on applicant's disclosure.* MPEP §2142 also states that impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. Additionally, ascertaining

the differences between the claimed invention and the prior art requires interpreting the claim language *and considering the invention and the prior art as a whole*. See MPEP § 2141.02.

Applicants respectfully submit that there is no suggestion or motivation in Castro *et al.*, alone or combined with knowledge generally available in the art, to modify the reference to arrive at the claimed invention, nor does it provide any reasonable expectation that modification of the morpholine ring to include methyl would successfully yield compounds having activity against IKK that would be useful for the diseases and disorders described by the Applicants. Applicants would also like to point out that in addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. See *In re Grabiak, 769 F.2d 729, 731-32 (Fed. Cir. 1985)*. Furthermore, Applicants respectfully assert that the Examiner must consider the prior art *as a whole*.

As stated previously, Castro *et al.*, when considered as a whole, teach away from the use of morpholine substituents. For example, in Table 4 (which lists a variety of analogues prepared along with their activity against IKK), compound **35**, the compound that is cited by the Examiner, has an IC_{50} of greater than 20, whereas other compounds that do not have the morpholine substituent (e.g., compound **33**) have increased activity (0.7 μM for compound **33**). Thus, in view of the disclosure of Castro *et al. as a whole*, one of ordinary skill in the art would not be motivated to select the morpholine substituent for modification, nor would they have any reasonable expectation that the use or modification of the morpholine substituent would successfully lead to compounds having increased activity as inhibitors of IKK. Similar to the situation in *Takeda Chemical Industries, Ltd.. v. Alphapharm Pty., Ltd.* , 492 F.3d 1350 (Fed. Cir. 2007), considering the subject invention as a whole would have directed one of ordinary skill in the art away from the modification of morpholino compounds, and thus the prior art does not provide the suggestion for making the specific molecular modifications necessary to achieve the claimed invention.

In view of the remarks detailed above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) of claims 1, 9, and 17 be withdrawn by the Examiner.

Provisional nonstatutory obviousness-type double patenting rejection:

The Examiner has provisionally rejected claims 1, 9, and 17 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 11/101,998. Applicants respectfully submit that the claims of the present application are in condition for allowance and respectfully request notification of such. Applicants also request withdrawal of the provisional nonstatutory double patenting rejection upon allowance of the pending claims. See MPEP § 804